PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

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PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	30.03.2004
Applicant's or agent's file reference P35633WO/KVC	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/GB 02/05927	24.12.2002	28.12.2001

Applicant
PSIMEI PHARMACEUTICALS PLC et al.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the international preliminary examining authority:	Authorized Officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Brandt, M Tel. +49 89 2399-2926

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference P35633WO/KVC	**FOR FURTHER ACTION**	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/GB 02/05927	International filing date *(day/month/year)* 24.12.2002	Priority date *(day/month/year)* 28.12.2001
International Patent Classification (IPC) or both national classification and IPC A61K41/00		
Applicant PSIMEI PHARMACEUTICALS PLC et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 8 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the opinion
   - II ☐ Priority
   - III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
28.07.2003	30.03.2004
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized Officer Vandenbogaerde, A Telephone No. +49 89 2399-7874

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/GB 02/05927

I. Basis of the report

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17))*:

Description, Pages

1-34 as originally filed

Claims, Numbers

1-53 as originally filed

Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   ☐ contained in the international application in written form.

   ☐ filed together with the international application in computer readable form.

   ☐ furnished subsequently to this Authority in written form.

   ☐ furnished subsequently to this Authority in computer readable form.

   ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   ☐ the description, pages:

   ☐ the claims, Nos.:

   ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 37-45,52 (with respect to industrial applicability), 50-53

   because:

   ☒ the said international application, or the said claims Nos. 37-45,52 with respect to industrial applicability relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 50-53 are so unclear that no meaningful opinion could be formed *(specify)*:

   see separate sheet

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	7-8,11-16,20-29,46-48
	No:	Claims	1-6,9-10,17-19,30-45
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-48
Industrial applicability (IA)	Yes:	Claims	1-36,46-48 - 37-45: see separate sheet
	No:	Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

III.1 Claims 37-45 and 52 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

III.2 Claims 50-53 do not meet the requirements of Article 6 PCT in that the matter for which protection is sought is not clearly defined. Consequently, no opinion will be formulated with respect to novelty, inventive step and industrial applicability.

Re Item V

Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1: WO 01 34196 A (BRANDSCH MATTHIAS ;FRANK WILLY (DE); ARNOLD MANFRED (DE); FLEIG WO) 17 May 2001 (2001-05-17)

D2: WO 00 44682 A (UNIV MISSOURI) 3 August 2000 (2000-08-03)

D3: TOKUMITSU H ET AL: 'CHITOSAN-GADOPENTETIC ACID COMPLEX NANOPARTICLES FOR GADOLINIUM NEUTRON-CAPTURE THERAPY OF CANCER: PREPARATION BY NOVEL EMULSION-DROPLET COALESCENCE TECHNIQUE AND CHARACTERIZATION' PHARMACEUTICAL RESEARCH, NEW YORK, NY, US, vol. 16, no. 12, 1999, pages 1830-1835, XP000951445 ISSN: 0724-8741

D4: WO 00 45826 A (UNIV MISSOURI) 10 August 2000 (2000-08-10)

D5: US-A-5 443 813 (HAINFELD JAMES F) 22 August 1995 (1995-08-22)

D6: DATABASE CA [Online] CHEMICAL ABSTRACTS SERVICE, COLUMBUS, OHIO, US; FUKUMORI, YOSHINOBU ET AL: 'Nano-particulate design and preparation for targeting and controled release of drugs' retrieved from STN Database accession no. 135:127058 XP002224876 & INTERNATIONAL CONFERENCE ON PROCESSING

MATERIALS FOR PROPERTIES, PROCEEDINGS, 2ND, SAN FRANCISCO, CA, UNITED STATES, NOV. 5-8, 2000 (2000) 453-458. EDITOR(S): MISHRA, BRAJENDRA;YAMAUCHI, CHIKABUMI. PUBLISHER: MINERALS, METALS & MATERIALS SOCIETY, WAR,

D7: THOMAS J ET AL: 'Dodeca(carboranyl)-substituted closomers: toward unimolecular nanoparticles as delivery vehicles for BNCT.' CHEM COMMUN (CAMB), (2001 SEP 21) (18) 1884-5., XP002224874

D8: ALI O. SEZER ET AL.: 'Chemical vapor deposition of boron carbide.' MATERIALS SCIENCE AND ENGINEERING, vol. B79, 2001, pages 191-202, XP002224875

- D1 discloses (cf. claims 1,5,10,14,16-18, example 4, page 4 line 30-pag 5 line 14, page 3 line 1 - page 4 line 1) particles having a particle size of 30-100 µm comprising polyethylene and water-insoluble neutron activatable element Thulium oxide used for treating tumours.
- D2 describes (cf. page 7 line 20 - page 8 line 17, page 11 line 2-5) radioactive glass microspheres having a particle size of 1-40 µm comprising a neutron activatable rare earth radioisotope used for treating malignant tumours and arthritis.
- D3 discloses (cf. abstract, page 1831 column 1 paragraph 3 - column 2 paragraph 2) the preparation of water-insoluble gadopentetic acid-loaded chitosan nanoparticles having a mean particle size of 462 nm for Gadolinium neutron capture therapy of tumours.
- D4 describes (cf. claims 1,24,25, page 6 line 6 - page 7 line 24) ceramic microspheres comprising a ceramic material and a therapeutic neutron-activatable compound used for the treatment of cancerous and tumour bearing tissue.
- D5 discloses (cf. claims 1-5, Figure 1, column 7 line 49-column 8 line 4) a biological delivery system comprising apoferritine as load-bearing structure loaded with the neutron capture element Uranium-235 and conjugated to a biospecific ligand used for neutron capture therapy of tumours.
- D6 describes (cf. abstract) nano-particulate systems for targeting and controlled release of drugs, namely lipid nano-emulsions, chitosan nanoparticles and thermosensitive acrylic nanoparticles.
- D7 discloses (cf. page 1884 column paragraph 3) closomers as a new class of polyhedral borane derivatives having a particle size of 3-100 nm for boron

neutron capture therapy of tumours.

- D8 describes (cf. abstract, page 193 column 2 paragraph 2) the medical use of the neutron capture element boron carbide.

V.1 Claims 1-29 and 30-31 - *Composition for use in medicine*: Novelty - Inventive step

V.1.1 The subject-matter of independent claims 1 and 30 relates to (a composition comprising) a water-insoluble nanoparticle comprising at least one neutron capture element in an inorganic form for use in medicine.
The subject-matter of independent claim 2 relates to a water-insoluble nanoparticle comprising (i) at least one neutron capture element in an inorganic form and (ii) a biocompatible outer layer (e.g. polymers, excipients, low molecular weight oligomers, natural products, surfactants), for use in medicine.

V.1.2 The subject-matter of independent claims 1 and 30 is not novel according to Article 33(2) PCT over the teaching of D1, D2, D3, D4, D6 or D7. These prior art documents all describe the medical use of water-insoluble nanoparticles comprising a compound capable of capturing neutrons.

V.1.3 The subject-matter of independent claim 2 is not novel according to Article 33(2) PCT over the teaching of D6. Document D6 (cf. abstract) describes nanoparticulate systems such as thermosensitive acrylic nanoparticles for gadolinium neutron capture therapy; thermosensitive acrylic nanoparticles comprise an acrylic composite latex with a hydrophobic core and a thermosensitively swellable shell.

V.1.4 Dependent claims 3-29 and 31 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step, taking into account that merely standard materials known to the skilled person are used for the preparation of nanoparticles.

V.2 Claims 32-36, 37-42 and 43-44 - *Therapeutical application*: Novelty - Inventive step

V.2.1 The subject-matter of claims 32-36, 37-42 and 43-44 relates to the therapeutical application of a composition comprising a water-insoluble nanoparticle comprising at least one neutron capture element in an inorganic form for neutron

capture therapy of cancer.

V.2.2 The subject-matter of independent claims 32, 37 and 43 is not novel according to Article 33(2) PCT over the teaching of D1, D2, D3, D4, D6 or D7. These prior art documents all describe the medical use of water-insoluble nanoparticles comprising a compound capable of capturing neutrons for the treatment of cancer.

V.2.3 Dependent claims 33-36, 38-42 and 44 do not contain any features which, in combination with the features of any claim to which they refer, meet the requirements of the PCT in respect of novelty and/or inventive step.

V.3 Claims 46-49 - *Process*: Novelty - Inventive step

V.3.1 The subject-matter of claims 46-49 relates to a process for preparing said water-insoluble nanoparticles.

V.3.2 The subject-matter of claims 46-49 is anticipated by the teaching of the prior art, since merely standard techniques known to a person skilled in the preparation of nanoparticles are used.

V.4 Industrial applicability

For the assessment of the present claims 37-45 and 52 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.